CASE REPORT

Pemphigus foliaceus associated with *Hypericum perforatum*

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INTRODUCTION

Pemphigus foliaceus is a rare autoimmune bullous dermatosis that can be induced by drugs, with variable duration lasting between several weeks and months. Erythematous scaly patches develop on the scalp, face, neck or chest.[1] The use of oral or topical herbal supplements to improve health has increased in the last decades. These preparations may trigger multiple adverse effects, both cutaneous and systematic.[2]

Hypericum perforatum (popularly known as St. John's wort) is an herbal drug with a widely known photosensitizing effect and a possible immunomodulatory effect.[2,3]

CASE REPORT

We present a 37-year-old woman, with no personal or family history of disease, who suffered from an pruritic rash on her trunk for 2 months. Initial lesions were small vesicles that rapidly developed into crusted erosions. One week before the appearance of skin lesions, she started taking St. John's wort orally (900 mg/d) as a remedy for fatigue associated with insomnia.

Cutaneous examination found several erosive crusted and well-defined patches with erythematous edges on her lower neck and upper back (Figs 1 and 2). No lesions appeared on the limbs, face, cheeks, mucous membranes, nails, and scalp. Nikolsky's sign was negative. After 1 week of treatment with Amoxicillin-clavulanate, 875/125 mg (1 tablet every 8 hours), and topical mupirocin (twice daily), there was no clinical improvement.

All the following laboratory evaluations were within the normal range: biochemical parameters, complete blood cell count, white blood cell count, differential count, urinalysis, erythrocyte sedimentation rate, serum protein electrophoresis, quantitative serum immunoglobulins, C3 and C4 levels, and rheumatoid factor. The following tests were negative: antinuclear antibodies, transglutaminase antibodies, anti–double-stranded DNA antibodies, and anti-Ro and anti-La antibodies. Venereal Disease Research Laboratory, hepatitis C, hepatitis B, HIV, and Mantoux tests were negative. Chest radiographs and abdominal ultrasound scans were taken with no pathologic findings.

Abbreviation used:
CYP: cytochrome P

A skin biopsy found an intra-epidermal blister and inflammatory dermal infiltrate composed of lymphocytes and eosinophils (Fig 3). Direct immunofluorescence on perilesional skin found deposits of IgG and C3 on keratinocytes' surface and along the dermo-epidermal junction (Fig 4). Enzyme-linked immunosorbent assay screening found a high titer of antidesmoglein 1 antibodies (108 U/mL) and low titer of antidesmoglein 3 antibodies (0.85 U/mL).

According to the clinical and diagnostic features, pemphigus foliaceus was diagnosed. Oral prednisone, 0.5 mg/kg/d and clobetasol propionate, 0.05% cream daily were prescribed; however, within 1 month there was no clinical improvement. Consequently, the patient was treated with azathioprine, 100 mg/d, and St. John's wort use was discontinued. After 2 months, the disease completely resolved with no residual skin damage. Azathioprine

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Fig 1. Crusted patch on her lower neck.

Fig 2. Pemphigus foliaceus. Scaly and crusted patches with erythematous edges on her upper back.

was discontinued after 10 months of remission. The patient had no new active skin lesions for 12 months, during which she didn't receive any treatment.

DISCUSSION

Topical and oral herbal supplements have been associated with several skin diseases[2-4] including urticaria, angioedema, allergic contact dermatitis, phototoxic rash, erythroderma, lichen planus, Sweet's syndrome, exudative erythema, Steven-Johnson syndrome, erythema nodosum, palmoplantar hyperkeratosis, skin ulcerations, and squamous cell carcinoma. The development of autoimmune diseases,[5,6] such as pemphigus vulgaris, dermatomyositis, and lupuslike syndrome, has been reported.

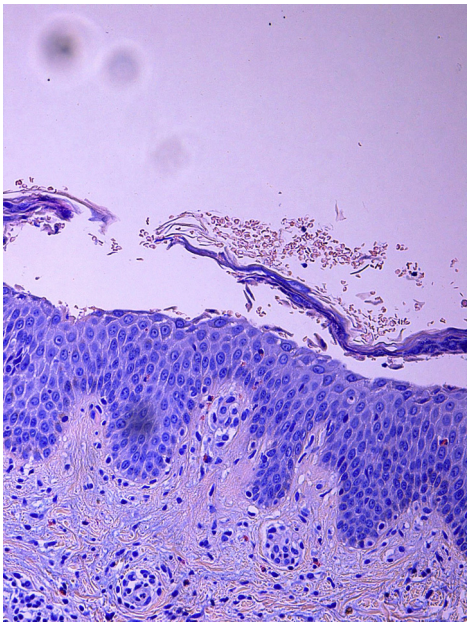

Fig 3. Intraepidermal subcorneal blister with acantholytic keratinocytes and eosinophils. Inflammatory superficial dermal infiltrate composed of lymphocytes and eosinophils (Hematoxylin-eosin stain; original magnification: ×20).

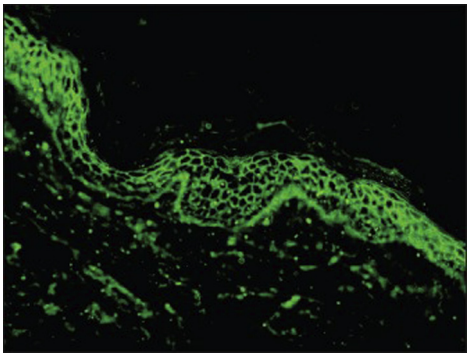

Fig 4. Direct immunofluorescence with deposits of IgG and C3 on keratinocytes' surface and along the dermo-epidermal junction.

Herbal supplements should be avoided during pregnancy or lactation and used with caution in patients with reduced liver or kidney function.[2-8]

H perforatum derives from *Hypericaceae* family plants and it has been used for more than 2000 years. It has several biologically active substances, namely hypericin and hyperforin. Other compounds include flavonoids, quercetin, kaempferol, xanthones, and bioflavonoids.[3]

H perforatum has been popularly used as a neuroprotective agent, as an antioxidant, and as a treatment for depression, anxiety, insomnia, water retention, cuts, burns, viral and bacterial diseases, inflammatory disorders, cancer, and opium dependence.[3,7]

H perforatum has an adverse event rate of 50%, the majority being mild to moderate and transient. The risk depends on several factors such as age, sex, genetics, nutritional status, comorbidities, and concurrent treatments.[3,7]

The most common adverse effects are gastrointestinal disturbances, allergic reactions, dizziness, headache, confusion, restlessness, lethargy, and dry mouth.[3,7] A very common side effect is phototoxicity[3,7,9] secondary to high doses of hypericin (≥ 0.5 mg/kg). The hypericin can absorb the ultraviolet light and the visible part of the electromagnetic spectrum. Phototoxicity can potentially induce eye damage and a pruritic skin rash. Phototoxicity is caused by photo-oxidation of components of the cell membrane (hypericin and pseudohypericin), causing active forms of oxygen including singlet oxygen, superoxide and hydroxyl radicals, and peroxides. Hypericin has been used as photosensitizer for photodynamic therapy of skin neoplasms.[9]

H perforatum may interact with other drugs. It can induce intestinal P-glycoprotein and liver cytochrome P450s (CYPs), including CYP2C9 and CYP3A4.[3,7,8,10]

Therefore, *H perforatum* may reduce the efficacy of the oral contraceptive pill, warfarin, proton-pump inhibitors, antihypertensives, benzodiazepines, immunosuppressants, digoxin, theophylline, carbamazepine, HIV medication (protease inhibitor), fluoroquinolones, tetracyclines, and analgesics. Moreover, *H perforatum* may potentiate the adverse effects of anesthetics, opioid, antidepressants (serotonin-specific reuptake inhibitors) and antidiabetic agents.[3,7,8,10]

Autoimmune diseases[2-7] may be triggered by an immune-enhancing effect. Herbal supplements may increase activity of macrophages, neutrophils, natural killer cells, and proinflammatory cytokines levels such as interleukin-1 and tumor necrosis factor—alpha. However, the mechanisms of action remain unknown.

Herbal supplements should be considered medications and health professionals should be aware of their potential adverse effects and drug interactions. Herbal supplements may have an immune-enhancing effect, exacerbating preexisting autoimmune diseases or triggering autoimmune disease in genetically predisposed individuals.[2-7] As a result, a complete drug history is necessary. In our case, pemphigus foliaceus onset was temporally associated with the use of *H perforatum*, but cause and effect cannot be proven. Further studies are needed to investigate the effect of herbal drugs in pemphigus and other autoimmune diseases.

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